REMARKS

Claims 1-12, 18, and 19 are pending. All pending claims are rejected under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102(a). Applicants address each basis for rejection below.

Claim Amendments

Claims 2, 4, 9, and 10 have been amended. In particular, claim 2 has been re-written in independent form. Support for the amendment to claim 2 is found, for example, at page 26, lines 14-28, of the specification as filed. Claims 4, 9, and 10 have been amended to correct minor formatting errors. No new matter has been added by the present amendments.

Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-12, 18, and 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants note that the indefiniteness rejection of claims 1, 11, and 12 appears to have been withdrawn. The particular indefiniteness rejections set forth in the Office Action are addressed as follows.

The Office asserts that claim 2 is indefinite because "the structure of the artificial chromosome is not clearly set forth" (Office Action, p. 2). The Office further states that claim 2 is "confusing because [the step] occurs prior to those in claim 1 but does not clearly set forth the structure of the cassette" and fails to "clearly set forth introducing the cassette into host cells" (Office Action, p. 3). Claim 2 has been re-written in independent form. Applicants submit that claim 2, as amended, is free of the indefiniteness rejection.

The Office asserts that claim 4 is indefinite because it "does not clearly further limit claim 2" (Office Action, p. 3). The Office requests that the features of claim 4 be

written in method format. Claim 4, as amended, sets forth additional method steps not required by claim 2. Applicants submit that claim 4, as amended, is free of this basis for rejection.

The Office asserts that claim 9 is indefinite for a lack of antecedent basis for the phrase "the activity of the protein encoded by a nucleic acid of interest that includes said first or second region of said endogenous chromosome," and that claim 10 is indefinite for a lack of antecedent basis for the phrase "the amount of functional protein." Applicants submit that, in view of the amendments to claims 9 and 10, the rejection under 35 U.S.C. § 112, second paragraph, of these claims should be withdrawn.

Rejection under 35 U.S.C. § 102(a)

Claims 1-12, 18, and 19 are rejected under 35 U.S.C. § 102(a) as being anticipated by Wilson et al. (*Anal. Biochem.* 296:270-278 (2001); hereafter "Wilson").

In response, Applicants direct the Office's attention to the enclosed Declaration of Dr. Brian Seed. Dr. Seed states (paragraph 2):

> Prior to September 15, 2001, I and the co-inventor, or individuals under my supervision carried out experiments that are described in the attached notebook pages (Exhibit 1; all dates have been redacted from Exhibit 1). Exhibit 1 describes the experimental methods used for characterization by fluorescence in situ hybridization (FISH) of ES cells into which an artificial chromosome has been inserted according to the methods described in the present application. In particular, the experiments were carried out by inserting into a mammalian cell an artificial chromosome containing a cassette that includes first and second regions of homology having at least 90% sequence identity to first and second regions of an endogenous chromosome of the mammalian cell and a selectable marker under conditions that result in homologous recombination between the artificial chromosome and the endogenous chromosome, resulting in integration of the cassette into the endogenous chromosome of the mammalian cell. As described in the specification (for example, at page 39, line 25, to page 40, line 29), and as illustrated in Figure 12 (copy enclosed as Exhibit 2) of the specification as filed, FISH analysis was used to confirm the proper

integration of the cassette in ES cells. Exhibit 1 describes the preparation of ES cells for FISH analysis, including hybridization with a probe specific for the inserted cassette, thereby confirming that a genetically modified mammalian cell had been produced in accordance with the presently claimed methods.

Thus, this Declaration demonstrates that Applicants reduced the presently claimed methods of producing genetically modified mammalian cells to practice prior to the September 15, 2001 publication date of the Wilson reference. The rejection of claims 1-12, 18, and 19 under 35 U.S.C. § 102(a) should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the final Office Action for one month, to and including August 11, 2008 because August 9th is a Saturday, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 11 August 2008

FOR

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